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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Griffith, et al.	Examiner:	Naff
Serial No.:	09/008, 945	Art Unit:	1651
Filing Date:	January 20, 1998	Express Mail No.:	EL744195976US
Title:	TISSUE FORMATION BY INJECTING A CELL-POLYMERIC SOLUTION THAT GELS IN VIVO		

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

APPELLANT'S BRIEF UNDER 37 CFR § 1.192

Real Party in Interest

The present application is assigned to the Children's Medical Center Corporation ("Children's") and the Massachusetts Institute of Technology ("MIT"). Assignments to Children's Medical Center Corporation are recorded at Reel 6626, Frame 0675 and Reel 6909, Frame 0292. An assignment to MIT is recorded at Reel 6909, Frame 0296.

Related Appeals and Interferences

No other appeals or interferences are known to the Appellant, the Appellant's legal representative, or the Appellant's assignee that will directly affect or be directly affected by the Board's decision in this appeal. Similarly, no such appeals or interferences are known that may have a bearing on the Board's decision in this appeal.

Status of Claims

Claims 25-52 are pending and stand rejected. Claims 1-24 have been cancelled. The rejection of claims 25-52 is hereby appealed.

Status of Amendments

All amendments proposed by the Appellant have been entered. The claims as currently pending appear in the Appendix to this Brief.

Summary of Invention

The invention is a method and implant for introducing cells into an animal (see, *e.g.*, page 2, lines 13-14). The implant is a hydrogel construct containing dissociated cells (see, *e.g.*, page 2, lines 22-23). After implantation, the construct is gradually remodeled into tissue that is similar in composition and histology to naturally-occurring tissue (page 2, lines 17-19). In one embodiment, exemplified by claims 25 and 35 and claims dependent thereon, cells are mixed with a solution of a biodegradable, biocompatible natural or synthetic organic polymer. The mixture is hardened to form a matrix having cells dispersed therein that is implanted into an animal. The hardened matrix has a desired anatomic shape (page 2, lines 23-28). In another embodiment, exemplified by claims 27, 36, and 44, and claims dependent thereon, cells are mixed with a solution of a biodegradable, biocompatible natural or synthetic organic polymer and introduced directly into a site in an animal, where the polymer hardens into a continuous three-dimensional open-lattice structure which entraps molecules to form a hydrogel containing the dissociated cells (page 2, lines 19-23). As recited by claim 46, the hydrogel may be partially hardened *ex vivo* and hardening completed *in vivo* (page 11, line 35, page 12, line 2). Claim 44 additionally recites that the dissociated cells are uniformly distributed in the hydrogel construct (see, *e.g.*, page 12, lines 29-32).

In one embodiment, the hydrogel is formed from alginate (see, *e.g.*, Example 1, page 12, line 21 *et. seq.*). For example, chondrocytes may be mixed with alginate dissolved in potassium phosphate buffer. Upon exposure to a multivalent ion, *e.g.*, calcium, or other hardening agent, the alginate solution hardens to form a hydrogel containing the chondrocytes. The hydrogel may be allowed to harden completely in a mold or other container and then implanted (page 12, lines 3-5). Alternatively, the cell-containing hydrogel may be administered to An animal before it is completely hardened (page 12, lines 35-39).

Alternative polymers are disclosed at page 4, lines 10 and 19-22, and recited in claims 28, 37, and 45. Methods of hardening the hydrogel are disclosed at page 3, line 37, page 4, line 12, and recited at claims 29, 30, 38, 40, 47, and 48. Exemplary ions that may be used to harden the hydrogels are disclosed at page 7, lines 28-36 and page 8, lines 12-14, and are recited in claims 31, 39, and 49. Exemplary cells that may be used with the invention are disclosed at page 10, lines 24-31 and are recited in claims 32-34, 41-43, and 50-52.

Issues

1. Whether claims 27-34 and 36-52 are unpatentable under 35 U.S.C. § 103(a) over U.S. Patent No. 5,294,466 to Schlameus (hereinafter "Schlameus") in view of U.S. Patent No. 5,266,326 to Barry (hereinafter "Barry"), PCT Publication WO92/19195 by Dionne (hereinafter "Dionne"), and U.S. Patent No. 5,354,736 to Bhatnagar (hereinafter "Bhatnagar").

2. Whether claims 25, 26, 28-35 and 37-43 are unpatentable under 35 U.S.C. § 103(a) over Schlameus in view of U.S. Patent Nos. 4,642,120 to Nevo (hereinafter "Nevo") and 5,041,138 to Vacanti (hereinafter "Vacanti A") and Vacanti, et al., "Selective cell transplantation using bioabsorbable artificial polymers as matrices," *Journal of Pediatric Surgery*, **23**: 3-9 (1988) (hereinafter "Vacanti B").

Grouping of Claims

Claims 25, 26, and 35 stand or fall together. Claims 27 and 36 stand or fall together. Claims 25, 26, and 35 are separately patentable from claims 27 and 36. These claims include different limitations that distinguish them from one another; they are also rejected over a different combination of references. Claims 25, 26, and 35 recite a hydrogel construct having a desired anatomic shape. No anatomic shape is recited in claims 27 or 36. In addition, claims 27 and 36 recite that a polymer is hardened following introduction into an animal. In contrast, the recitations of claims 25 and 35 require that the hydrogel construct have a desired anatomic shape prior to implantation.

Claims 28-34 stand or fall together. These claims depend from both claim 25 and claim 27. Claims 28-34 stand or fall together with claim 25 as they depend from claim 25. Claims 28-34 stand or fall together with claim 27 as they depend from claim 27.

Claims 37-43 stand and fall together. These claims depend from independent claims 35 and 36. Claims 37-43 stand or fall together with claim 35 as they depend from claim 35. Claims 37-43 stand or fall together with claim 36 as depend from claim 36.

Claims 44-52 stand or fall together. Claims 44-52 are separately patentable from claims 25, 26, and 35 and the claims that depend therefrom. Claims 25, 26, and 35 recite a hydrogel construct having a desired anatomic shape, which anatomic shape is not recited in claim 44 or the claims depending therefrom. Claims 44-52 are separately patentable from claims 27 and 36 and the claims depending therefrom because claim 44 recites a hydrogel construct in which dissociated cells are uniformly distributed. Claims 27 and 35 and the claims depending therefrom do not require a uniform distribution of cells within the recited hydrogel construct. As noted below, even the cited prior art references that disclose a hydrogel that encapsulates cells do not suggest a microscopic hydrogel construct having cell uniformly distributed therein.

Argument

The Cited Art

Schlameus discloses the use of microcapsules having a diameter between 500 and 1,000 μm to encapsulate cells. The microcapsules may be injected into a wound site or delivered by a donut-like support vehicle. Nevo describes a mixture of cells, fibrinogen, a protease-inhibitor, and thrombin that is pressed into a wound site to fill a defect. Vacanti A discloses methods of preparing matrices of polymer fibers onto which cells may be seeded. Vacanti B discloses experiments in which cells are seeded on polymer discs or within fibrous networks. Vacanti B further discusses the use of polymer discs and branching fiber networks to facilitate nourishment of implanted cells. Barry discloses a method for preventing intra-articular adhesions by injecting alginate hydrogels into the joint. Dionne discloses a vehicle for the implantation of cells or other biologically active moieties comprising a core region containing

the cells and a peripheral region that surrounds the cells but does not contain any cells itself. Bhatnagar discloses the use of a specific polypeptide sequence to promote wound healing; the polypeptide sequence may be combined with a gel, *e.g.*, agarose.

Claims 25 and 35 Meet the Requirements of 35 U.S.C. § 103(a)

Independent claims 25 and 35, and claims dependent thereon, are not rendered obvious by Schlameus, Nevo, Vacanti A or Vacanti B, whether considered separately or in any combination, because these references do not suggest the production or use of a continuous three-dimensional open-lattice structure and a hydrogel construct having a desired anatomic shape.

Schlameus fails to disclose a continuous three-dimensional open-lattice structure. When implanted, the microcapsules (see, *e.g.*, column 4, lines 36-37) of Schlameus are merely an assemblage of microcapsules, not a hydrogel construct including a polymer having a continuous three-dimensional open-lattice structure. On a microscopic level, the injected microcapsules of Schlameus form a heterogeneous, discontinuous structure interrupted by the interstices between the microcapsules. Furthermore, the microcapsules may be prepared with a coating (column 5, lines 2-4) that introduces further discontinuity into the implant. In contrast, claims 25 and 35 require a polymer having a continuous, three-dimensional open-lattice structure.

Schlameus also fails to disclose a desired anatomic shape, as reflected in claims 25 and 35. The Examiner notes that "An anatomic shape does not have to be that of a whole body part or organ such as an ear, but can be the shape of any tissue to be replaced in the body" (Paper No. 96, page 7, lines 22-24). Even if the Examiner is correct in this statement, there is no structure in the body that is shaped as a bundle of microcapsules or even a single microcapsule. Thus, Schlameus fails to disclose or suggest an anatomic shape.

Nevo, Vacanti A, and Vacanti B, fail to remedy the failure of Schlameus to disclose a desired anatomic shape. Nevo discloses the production of a gel by combining fibrinogen, thrombin, a protease inhibitor, and cells. This material is pressed into a wound site to fill a defect (column 3, lines 60-61). The Examiner states that the gel "must be substantially the shape of the injured site or it would not be pressed into the site" (Paper No. 96, page 7, lines 2-3). However, the disclosure of Nevo does not state that the gels have any shape at all before being

pressed into the wound site. Rather, Nevo suggests that the gels may be stored before implantation. One skilled in the art would expect that the gels would be stored in a flask, jar, or similar container. A portion of the gel would be scooped up with a spatula and pressed into a wound site much like putty. Thus, the only shape that the gel might possibly have before implantation is the shape of the container in which it is stored. If the container were tipped, flow would cause the "shape" of the gel to change. Thus, Nevo does not disclose or suggest a "desired anatomic shape," as recited by claims 25 and 35.

Neither Vacanti A nor Vacanti B suggest hardening a polymer into an anatomic shape. The Examiner states that neither Vacanti A nor Vacanti B would "lead one to believe that a hydrogel can not be molded" (Paper No. 96, page 7, lines 11-12). However, these references do not suggest molding a hydrogel, neither to they suggest a method that might be successful in shaping a hydrogel. Even the discs or filaments of Vacanti A and Vacanti B must be further cut or otherwise manipulated to render them into a predefined shape. For example, the synthetic suture material disclosed in Vacanti A was cut into pieces, unbraided, and knotted before implantation (column 8, lines 4-7).

The Examiner further states that Vacanti A and Vacanti B suggest molding the hydrogel of Schlameus and the thrombin gel of Nevo into the shape of tissue being replaced before implantation. Neither Vacanti A nor Vacanti B remedy the failure of Schlameus to disclose hardening a polymer into a three-dimensional open-lattice structure which entraps water molecules, as recited by claims 25 and 35. Vacanti A and Vacanti B both disclose various methods of producing discs or filaments of polymer fibers (Vacanti A, column 6, lines 24-33; Vacanti B, page 3, right hand column). None of these discs include a hydrogel. A hydrogel entraps water molecules, while the shaped polymers of Vacanti A and Vacanti B are dry. Indeed, these references disclose that any solvent used should be evaporated (*e.g.*, Vacanti A, column 6, lines 26-27). Neither Vacanti A nor Vacanti B disclose any method of forming a hydrogel. Because water is incompressible, the disclosed techniques of compression molding and meshing are more likely to make a mess than a shape when applied to a polymer solution (see Vacanti A, column 6, lines 28-29 and 32-33). The thin film produced by solvent casting and the filaments produced by filament drawing are not three-dimensional structures as recited by

claims 25 and 35 of the present application (see Vacanti A, column 6, lines 24 and 27 and 30-31).

None of the references applied by the Examiner disclose or suggest "hardening a polymer into a continuous three-dimensional open-lattice structure which entraps water molecules to form a hydrogel construct containing the dissociated cells and having a desired anatomic shape" (claim 25). The prior art must provide a clear and particular suggestion, teaching, or motivation to combine the cited references to render obvious the claimed invention. In re Dembiczak, 175 F.3d 994, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). Indeed, there is nothing in either Vacanti A or Vacanti B except for hindsight reconstruction to suggest that either reference might be applied to a hydrogel instead of dry fibers. Nevo's disclosure that a gel may be molded *during* implantation and Schlameus' spherical microcapsules do not render obvious the formation of a hydrogel having a desired anatomic shape *before* implantation. Claims 25 and 35 and the claims depending therefrom are patentable over Schlameus, Nevo, Vacanti A, and Vacanti B.

Claims 27, 36, and 44 Meet the Requirements of 35 U.S.C. § 103(a)

Independent claims 27, 36, and 44, and claims dependent thereon, are not rendered obvious by Schlameus, Barry, Dionne, or Bhatnagar, whether considered separately or in any combination, because these references do not suggest the production or use of a continuous three-dimensional open-lattice structure including a polymer that may be hardened after implantation of a hydrogel for the purpose of forming tissue.

As noted above, Schlameus fails to disclose a continuous three-dimensional open-lattice structure. Furthermore, Schlameus fails to disclose a hydrogel construct in which dissociated cells are uniformly distributed, as recited by claim 44. Instead, Schlameus discloses a mass of microcapsules. There are no cells in the interstitial spaces between the microcapsules when they are implanted. In addition, there are no cells in the optional coating (see column 5, lines 2-4). As noted by the Examiner, the gel within the microcapsules of Schlameus is hardened before implantation into an animal, not at least partially following implantation as required by claims 27, 36, and 44 (Paper No. 96, page 4, line 13-14).

Barry fails to remedy the failure of Schlameus to disclose a hydrogel construct including a continuous three-dimensional open-lattice structure and dissociated cells. Indeed, Barry fails to disclose that any cells should be combined with the hydrogel at all.

In addition, there is no motivation to combine the teachings of Barry and Schlameus. Barry discloses preventing the formation of adhesions within joints (column 1, line 12). The Examiner states, "It would have been obvious to omit forming microcapsules and inject the cell-containing alginate solution of Schlameus et al into intra-articular space as suggested by [Barry] et al to allow *in situ* gel formation to prevent intra-articular adhesions" (Paper No. 96, page 3, lines 23-26). However, there is no motivation to inject the microcapsules of Schlameus according to the method of Barry because the microcapsules of Schlameus are already injectable (column 4, lines 38-39). Furthermore, even if there was motivation to make the combination, one skilled in the art would not reasonably expect success from doing so. Barry teaches injection under conditions that *avoid* tissue formation. The present claims recite methods that include tissue formation. Cells entrapped within the hydrogels of the present invention are intended to produce collagen, a component of the adhesions whose formation Barry is trying to prevent. There can be no motivation to combine two references or to modify a reference if the modification would thwart the intended purpose of the cited reference. MPEP 2143.01, citing In re Gordon, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). Because the goals of Barry are opposed to the purpose of the invention and contrary to the recitations of claims 27, 36, and 44, there is no motivation to modify the teaching of Barry to achieve the method and implant of the pending claims.

Likewise, Dionne fails to disclose or suggest a method or implant for the formation of tissue. Indeed, Dionne fails to remedy the failure of Schlameus to disclose a hydrogel construct in which dissociated cells are uniformly distributed, as recited by claim 44. Instead, Dionne discloses an immunoisolatory vehicle including a core which retains cells or another biologically active moiety and a surrounding jacket which is free of cells and which isolates the core from the surrounding tissue and protects it from immunological attack (page 16, lines 14-22, 24). The cells are intended to provide a biological product or to perform a metabolic function (page 10, lines 24-27). However, the released products are not intended to be extracellular matrix

components, but rather growth factors or other metabolic regulators such as insulin. Even where fibroblasts, collagen-producing cells, are encapsulated within a construct, it is to produce a recombinant protein (page 43, lines 30-32).

Dionne also distinguishes the macrocapsules of his disclosure from microcapsules described in the prior art. On page 8, Dionne calls the release of encapsulated cells from microcapsules a disadvantage (lines 12-16). At pages 46-47, Dionne again distinguishes his device from microcapsules and critiques microcapsules for their susceptibility to deterioration (page 47, line 23). However, Schlameus discloses that the encapsulated cells are meant to be released eventually. While the rate of release should be controlled (page 4, lines 66-68), it does not need to be prevented. The microcapsules of Schlameus are supposed to degrade (see, *e.g.*, column 13, lines 28-41, referring to the microcapsules as "artificial cells"). Likewise, the hydrogels of the invention are gradually remodeled as the cells within them both produce new tissue and enzymes that gradually degrade the hydrogel. As for Barry, combination of the teachings of Dionne and Schlameus would thwart the purposes of one or the other. See id. Furthermore, Dionne teaches against the use of microcapsules or the application of his disclosure for use with microcapsules. As a result, there is no motivation to combine the teachings of Dionne and Schlameus.

Bhatnagar fails to provide motivation to combine the teachings of Dionne and Barry with those of Schlameus. While Bhatnagar promotes the use of hydrogels for tissue reconstruction (column 12, line 38; abstract), he also teaches that the peptide sequences disclosed in the patent are necessary to prevent the formation of fibrous scar (column 6, line 61-64). Dionne teaches that microcapsules are particularly prone to the formation of fibrous tissue (page 47, line 22). There is nothing in any of the cited references to indicate that cells in a macroscopic matrix would be able to promote proper tissue formation in the absence of peptides. The Examiner equates the functions of encapsulation as disclosed by Schlameus with the function of the peptides disclosed by Bhatnagar (Paper No. 96, page 5, lines 13-16). The Examiner suggests that the disclosure of Bhatnagar makes it clear that the use of a microcapsule is not essential for cells to form tissue, stating, "Entrapment can occur in the same way when hardening occurs *in vivo* as when the hydrogel is formed prior to implanting" (Paper No. 96, page 5, lines 16-18).

However, the combination of Schlameus and Bhatnagar only suggests that microcapsules should be replaced by a peptide. The disclosures of Bhatnagar do not suggest that the cells are retained when the hydrogel is hardened *in vivo* because a macroscopic gel is used instead of microcapsules. Rather, Bhatnagar discloses that if the disclosed peptide sequences are used, cells will migrate into the gel whether it is hardened *in vivo* or *ex vivo* (column 13, lines 50-60). As a result, the teachings of Bhatnagar do not provide motivation to combine Barry and Dionne with Schlameus. Furthermore, there is no motivation to combine Bhatnagar with Schlameus to form a macroscopic hydrogel construct containing a continuous three-dimensional open-lattice structure and dissociated cells as provided by the instant invention because Bhatnagar teaches that a macroscopic (unencapsulated) hydrogel including cells is far inferior to the peptide-containing gels disclosed by Bhatnagar (column 14, lines 53-56).

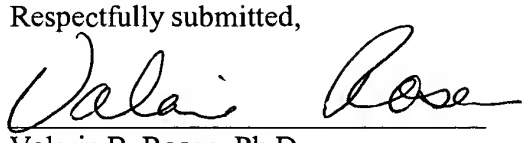
In addition, because Bhatnagar discloses that cells migrate into the disclosed gels from the surface (see, *e.g.*, column 12, lines 40-41), he fails to remedy the failure of Schlameus to disclose or suggest a hydrogel construct in which cells are uniformly distributed, as recited by claim 44. Even assuming that cells are able to migrate into the gels of Bhatnagar before hardening is completed (see column 13, lines 58-60), there is no suggestion in Bhatnagar that cells would distribute themselves evenly throughout the matrix before gelation was complete (see, *e.g.*, page 12, lines 28-29 of the instant application, disclosing that the hydrogel only needs 30-45 mins. to harden).

Conclusion

Applicant submits that all pending claims are patentable under 35 U.S.C. §103(a). Reversal of all outstanding rejections and allowance of the pending claims is therefore earnestly requested.

A check for $320.00 to cover the fee set by 37 C.F.R. §1.17(c) is enclosed. Please charge any fees associated with this filing, or apply any credits, to our Deposit Account No. 03-1721.

Respectfully submitted,



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APPENDIX

25. A method for introducing cells into an animal to form tissue, comprising:

forming a cell-polymeric composition by mixing dissociated cells with a solution of a biodegradable, biocompatible natural or synthetic organic polymer;

hardening the polymer into a continuous three-dimensional open-lattice structure which entraps water molecules to form a hydrogel construct containing the dissociated cells and having a desired anatomic shape; and

introducing said hydrogel construct into the animal.

26. The method of claim 25, further comprising introducing said cell-polymeric composition into a mold having a desired anatomic shape prior to the step of hardening.

27. A method for introducing cells into an animal to form tissue, comprising:

forming a cell-polymeric composition by mixing dissociated cells with a solution of a biodegradable, biocompatible natural or synthetic organic polymer;

introducing said cell-polymeric composition into the animal; and

following the step of introducing, hardening the polymer into a three-dimensional open-lattice structure which entraps water molecules to form a hydrogel containing the dissociated cells.

28. The method of claim 25 or 27, wherein the natural or synthetic organic polymer is selected from the group consisting of alginate, polyphosphazines, polyethlene oxide-propylene

glycol block copolymers, poly(acrylic acids), poly(methacrylic acids), copolymers of acrylic acid and methacrylic acid, poly(vinyl acetate), and sulfonated polymers.

29. The method of claim 28, wherein hardening comprises cross-linking the polymer with multivalent ions.

30. The method of claim 25 or 27, wherein hardening comprises exposing the polymer to an agent selected from the group consisting of ions, pH changes, and temperature changes.

31. The method of claim 30, wherein hardening comprises allowing the polymer to interact with ions selected from the group consisting of copper, calcium, aluminum, magnesium, strontium, barium, tin, and di-, tri- or tetra-functional organic cations; anions selected from the group consisting of low molecular weight dicarboxylic acids, sulfate ions and carbonate ions.

32. The method of claim 25 or 27, wherein the cells are selected from the group consisting of cells that form cartilage, cells that form bone, muscle cells, fibroblasts, and organ cells.

33. The method of claim 32, wherein the cells that form cartilage comprise chondrocytes.

34. The method of claim 32, wherein the cells that form bone comprise osteoblasts.

35. An implant for introducing cells into an animal, said implant being a cell-polymeric composition comprising: dissociated cells and a biodegradable, biocompatible natural

or synthetic organic polymer, wherein the polymer hardens into a continuous three-dimensional open-lattice structure which entraps water molecules to form a hydrogel construct containing said dissociated cells, said hydrogel construct having a desired anatomic shape.

36. An implant for introducing cells into an animal to form tissue, said implant being a cell-polymeric composition comprising: dissociated cells and a biodegradable, biocompatible natural or synthetic organic polymer, wherein the polymer hardens into a three-dimensional open-lattice structure which entraps water molecules to form a hydrogel construct containing said dissociated cells, said cell-polymeric composition being suitable for implantation into an animal before hardening.

37. The implant of claim 35 or 36, wherein the natural or synthetic organic polymer is selected from the group consisting of alginate, polyphosphazines, polyethylene oxide-polypropylene glycol block copolymers, poly(acrylic acids), poly (methacrylic acids), copolymers of acrylic acid and methacrylic acid, poly(vinyl acetate), and sulfonated polymers.

38. The implant of claim 37, wherein the cell-polymeric composition can be hardened by exposure to an agent selected from the group consisting of ions, pH changes, and temperature changes.

39. The implant of claim 38, wherein the cell-polymeric composition can be hardened by interaction with ions selected from the group consisting of copper, calcium, aluminum, magnesium, strontium, barium, tin, and di-, tri- or tetra-functional organic cations; or anions

selected from the group consisting of low molecular weight dicarboxylic acids, sulfate ions and carbonate ions.

40. The implant of claim 37, wherein the cell-polymeric composition is hardened by cross-linking the polymer with multivalent ions.

41. The implant of claim 35 or 36, wherein the dissociated cells are selected from the group consisting of cells that form cartilage, cells that form bone, muscle cells, fibroblasts, and organ cells.

42. The implant of claim 41, wherein the cells that form cartilage comprise chondrocytes.

43. The implant of claim 41, where the cells that form bone comprise osteoblasts.

44. A method for introducing cells into an animal to form tissue, comprising:

forming a cell-polymeric composition by mixing dissociated cells with a solution of a biodegradable, biocompatible natural or synthetic organic polymer;

introducing said cell-polymeric composition into the animal; and

hardening the polymer into a three-dimensional open-lattice structure which entraps water molecules to form a hydrogel construct in which the dissociated cells are uniformly distributed,

wherein the step of hardening is completed after introduction of said cell-polymeric composition into the animal.

45. The method of claim 44, wherein the natural or synthetic organic polymer is selected from the group consisting of alginate, polyphosphazines, polyethlene oxide-propylene glycol block copolymers, poly(acrylic acids), poly(methacrylic acids), copolymers of acrylic acid and methacrylic acid, poly(vinyl acetate), and sulfonated polymers.

46. The method of claim 44, wherein the step of hardening is initiated to partially harden the polymer before the step of introducing.

47. The method of claim 44 or 46, wherein hardening comprises cross-linking the polymer with multivalent ions.

48. The method of claim 44 or 46, wherein hardening comprises exposing the polymer to an agent selected from the group consisting of ions, pH changes, and temperature changes.

49. The method of claim 48, wherein hardening comprises allowing the polymer to interact with ions selected from the group consisting of copper, calcium, aluminum, magnesium, strontium, barium, tin, and di-, tri- or tetra-functional organic cations; anions selected from the group consisting of low molecular weight dicarboxylic acids, sulfate ions and carbonate ions.

50. The method of claim 44, wherein the cells are selected from the group consisting of cells that form cartilage, cells that form bone, muscle cells, fibroblasts, and organ cells.

51. The method of claim 50, wherein the cells that form cartilage comprise chondrocytes.

52. The method of claim 50, wherein the cells that form bone comprise osteoblasts.